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EXAMINER

SCHLIENTZ, LEAH H

ART UNIT PAPER NUMBER

1618

MAIL DATE DELIVERY MODE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/693,252

Applicant(s)

MEADE ET AL.

Examiner

Leah Schlientz

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 June 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 19-36 is/are pending in the application.
- 4a) Of the above claim(s) 23, 24, 26-28 and 30-36 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 19-22, 25 and 29 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 24 October 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application
- ☐ Other: _____

DETAILED ACTION

Election/Restrictions

Applicant's election of the following species in the reply filed on 6/20/2007 is acknowledged: SEQ ID No. 4 as the MMP peptide and p-aminobenzyl as the linker. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 19 – 36 are pending. Claims 31 – 36 are newly added. Applicant contends on page 6 of the Response that "Applicants do not believe an election of species between the compounds of claims 19, 20 and 31 is required. However, if an election of species is deemed necessary, Applicants hereby elect the compound of Claim 31." However, newly added claim 31 is a distinct species to that of original claims 19 and 20, which were pending at the time of the mailing of the Office Action, mailed 4/2/2007, and therefore would have required additional consideration by the examiner regarding a further species election to be included in the Office Action, such as the position of the peptide on the macrocycle, etc, had they been present at the time the Office Action was mailed. Accordingly, newly added claims 31 – 36 are withdrawn from consideration at this time by the examiner. Claims 19 – 22, 25 and 29 are readable upon the originally requested single disclosed species having a defined peptide sequence and linker, and are examined herein on the merits for patentability.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19 and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to a method, comprising administering an MRI agent having the formula: a metal DOTA chelate conjugated to $X_1-(Y_1)_n\text{-Ala-Leu-}(Y_2)_m$, where Y_1 and Y_2 are independently amino acid moieties, and n and m are independently an integer from 0 to 5. Such a peptide sequence results in literally millions upon millions of potential sequences (i.e. each Y_1 and Y_2 may independently represent 20^5 structures, not to mention the exponential number of possibilities of sequences which result from their various combinations). However, applicant has provided examples of only a few representative peptide sequences which correspond to the claimed genus (i.e. SEQ. ID 1 – 4, as well as the sequences provided in Example 1, paragraphs 243 – 270). Such a limited disclosure of a few representative species does not provide support that applicant has possession of a reasonable number of species of the claimed genus to substantiate claiming such a broad genus which may include millions and millions of potential species.

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The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps. See MPEP § 2172.01. The claims are drawn to a method, comprising administering an MRI agent. The metes and bounds of the invention are indefinite because it is not clear what the method is to be accomplished via the claimed method.

Claims 20, 22, 25 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. For example, the claims are drawn to a method comprising administering an MRI agent that contains a metal DOTA chelate- X_1 -MMP peptide- $(X_2)_p$. X_1 and X_2 are defined as independent linkers. The claim is confusing because X_2 appears to occupy a terminal position on the compound, and thus it is unclear what it is to link.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section

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351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 20, 22, 25 and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Lauffer *et al.* (US 6,709,646).

Lauffer discloses improved diagnostic agents for Magnetic Resonance Imaging and optical imaging. In particular, MRI and optical imaging agents that allow for the sensitive detection of a specific bioactivity within a tissue are disclosed. The agents are prodrug contrast agents which are bioactivated in vivo in the presence of the specific bioactivity (abstract). The prodrugs must comprise three domains: an image-enhancing moiety (IEM), a modification site (MS), and a protein binding moiety (PBM) (column 4, lines 34 – 37). A preferred method of bioactivating the contrast agents includes the enzymatic cleavage of the prodrug at the MS (column 4, lines 49 – 50). When the contrast agents bind to a protein, there is a change in the IEM signal characteristic, such as a change in induced relaxation rates of water protons or a shift in one or more peaks or alteration in signal intensity in the NMR spectrum (column 6, lines 55+). The image-enhancing moiety may be gadolinium (III) chelate of DOTA (column 8, lines 43+ - column 9, line 10 or column 20, lines 55+). The protein binding moiety (PBM) may be a peptide (column 10, line 8). The modification site (MS) is a domain on the prodrug which is altered by the specific bioactivity desired to be imaged, such a biotransformation, enzymatic or otherwise, may include bond cleavage, etc. (column 15, lines 18 – 29). Preferred MSs are those which are altered by matrix metalloproteinases (MMPs), including MMP-7 (column 18, lines 14 – 37). Another particular example is

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that of MMP-1, wherein the protein binding moiety is represented by Gly-Ile-Arg-Lys and the modification site is the bond between Gly and Ile (column 19, lines 1 – 30).

Regarding claim 25, the agents may further comprise a masking moiety (MM) (see column 4, lines 51 – 56 and column 5, line 1), which may include a carbohydrate moiety (column 20, line 18).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 19 – 22, 25 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lauffer *et al.* (US 6,709,646) in view of Netzel-Arnett *et al.* (*Biochem.*, 1993, 32, p. 6427 – 6432).

Lauffer discloses prodrugs for MRI or optical imaging comprising three domains: an image-enhancing moiety (IEM), a modification site (MS), and a protein binding

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moiety (PBM) (column 4, lines 34 – 37), as set forth above. The image-enhancing moiety may be gadolinium (III) chelate of DOTA (column 8, lines 43+ - column 9, line 10 or column 20, lines 55+). Preferred MSs are those which are altered by matrix metalloproteinases (MMPs), including MMP-7, or matrilysin (column 18, lines 14 – 37).

Lauffer does not specifically recite that the protein binding moiety and modification site are a peptide sequence including $X_1-(Y_1)_n\text{-Ala-Leu-(Y}_2)_m$, where Y_1 and Y_2 are independently amino acid moieties, and n and m are independently an integer from 0 to 5, or applicant's elected species SEQ. ID. No. 4 (Pro-Met-Ala-Leu-Trp-Met-Arg).

Netzel-Arnett discloses that MMP (matrix metalloproteinases) are a family of enzymes that are believed to play a leading role in both the normal turnover and pathological destruction of the extracellular matrix (page 6427). Matrilysin, or PUMP-1 (i.e. MMP-7) hydrolyzes proteoglycans, fibronectin, laminin, gelatin and other substrates (page 6428, left column). The homologous MMP family of proteinases can exhibit diversity in their protein substrate specificity. Netzel-Arnett studied the sequence specificity of PUMP and two other proteinases (HFC and HNC) in order to elucidate the contribution of sequence specificity to protein specificity, important to the design of optimized synthetic substrates and inhibitors (page 6428, left column). Peptides 1 – 58 were prepared and compared to a reference octapeptide which is modeled after the collagenase cleavage site of calf/chick $\alpha 1(1)$ chain of collagen. Kinetic parameters for the hydrolysis of these peptides by PUMP, HFG and HNG were determined (page 6428). PUMP exhibits a strong preference for Leu in subsite P_1' (page 6431, left

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column and Table 5). Synthetic substrates were prepared and tagged with a fluorescent Trp residue in subsite P₂', a dinitrophenyl quenching group on the N-terminus, and an Arg residue for enhanced solubility in subsite P₄'. Quenching of the Trp fluorescence by the DNP group in the intact peptide is relieved on hydrolysis of the P₁-P₁' bond for a continuously recording fluorescent assay (page 6431, left column). A good candidate substrate for PUMP is DNP-Pro-Met-Ala-Leu-Trp-Met-Arg.

Netzel-Arnett teaches the PUMP, or MMP-7, substrate Pro-Met-Ala-Leu-Trp-Met-Arg to be conjugated to a fluorescent moiety (DNP), rather than an MRI chelate agent.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute the MMP-7 substrate, Pro-Met-Ala-Leu-Trp-Met-Arg, taught by Netzel-Arnett, for the MMP-1 substrate, Gly-Ile-Arg-Lys, in the bioactivatable contrast agents of Lauffer in order to provide a suitable cleavage site for the MMP enzyme, as taught by Lauffer (see Table IV and column 19 of Lauffer). Lauffer teaches that a variety of MMP enzymes may be employed as suitable cleaving agents, including both MMP-1 and MMP-7. One would have been motivated to do so because Lauffer reasonably teaches a bioactivatable contrast agent wherein the agent comprises and MMP modification site cleavable by MMP-7, however, Lauffer does not teach an MMP-7 specific substrate sequence, therefore one would be motivated to use the substrate taught by Netzel-Arnett as a suitable MMP-7 cleavage site. One would reasonably expect successful cleavage because Netzel-Arnett teaches such properties.

Conclusion

No claims are allowed at this time.


The following reference is considered relevant to the instant invention is made of record, but is not relied upon for rejection at this time: Decicco *et al.* (US 6,989,139).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LHS


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